Please amend this application as follows: (MPEP 608.01j and 37 C.F.R. 1.126 require that the claim numbering following the numbering of the last submitted claim (whether entered or not)).

Cancel Claims 47-61 and add Claims 62-72

62. Flat rod shaped or plate-like crystals of a peptide having the amino acid sequence of SEQ ID NO:X prepared by crystallizing the peptide from an aqueous solution comprising the peptide and between about 2-15% ethanol (v/v) or between about 2-15% propanol (v/v) and wherein the solution optionally comprises ammonium sulfate or a soluble zinc salt and provided that the crystals vary in size from between about 2-25 microns by 10-150 microns with a depth from about 0.5-5 microns.

63. The crystals of Claim 62 wherein the concentration of the peptide in the solution is between about 1-10 mg/ml and the pH of the solution is between about 6 and 7.

64. The crystals of Claim 63 wherein the concentration of peptide in the solution is between about 2-7 mg/ml and the solution comprises between about 3-13% ethanol (v/v).

65. The crystals of Claim 64 wherein the solution comprises ammonium sulfate at a concentration of about 1% (w/v).

66. The crystals of Claim 62 wherein the concentration of peptide in the solution is between about 1-20 mg/mL, the molar ratio of zinc to peptide is between about 0.5 to 1.7, and the pH of the solution is between about 7-10.

67. The crystals of Claim 66 wherein the concentration of

peptide in the solution is between about.2-10 mg/mL, the molar ratio of zinc to peptide is between about 0.6 to 1.5, and the pH of the solution is between about 7.2-9.7.

68. Flat rod shaped or plate-like crystals of a peptide having the amino acid sequence of SEQ ID NO:X prepared by crystallizing the peptide from an aqueous solution comprising the peptide and between about 2-15% (weight as a percent of total volume) of a monosaccharide or disaccharide selected from the group consisting of: a) trehalose; b) mannitol; c) glucose; d) erythrose; e) ribose; f) galactose; g) fructose; h) maltose; i) sucrose; and j) lactose; and wherein the solution optionally comprises ammonium sulfate or zinc and provided that the crystals vary in size from between about 2-25 microns by 10-150 microns with a depth from about 0.5-5 microns.

69. The crystals of Claim 68 wherein the disaccharide is trehalose.

70. The crystals of Claim 68 wherein the monosaccharide is mannitol.

71. A composition comprising the crystals of Claim 62.

72. A composition comprising the crystals of Claim 68.

73. The composition of Claim 71 wherein the composition additionally comprises zinc.

74. The composition of Claim 72 wherein the composition additionally comprises zinc.

Remarks

Applicants submit that the amended claim set

presented above is fully supported by the specification and presents no new matter. The claims have support throughout the specification as originally filed. For example:

Claim 62:

Claim 62 has been amended to replace Val-8-GLP-1(7-37)OH with SEQ ID NO:X. SEQ ID NO:2 in the current sequence listing specifies a genus of GLP-1 analogs that includes the Val-8 species. The sequence listing has been updated to specifically assign the Val-8 species with a SEQ ID NO. The sequence of Val-8-GLP-1(7-37)OH was provided in the specification as originally filed. The sequence of GLP-1(7-37)OH is provided on page 5, line 9 and labeled SEQ ID NO:1. Val-8-GLP-1(7-37)OH is listed on page 5, line 19. The nomenclature is described on page 4, line 31 through p. 5, line 5. The amino terminus is assigned residue 7. Thus, Val-8-GLP-1(7-37)OH is GLP-1(7-37)OH [SEQ ID NO:1] wherein valine is substituted for the wild-type residue at position 8. Furthermore, SEQ ID NO:2 provides a formula for GLP-1 analogs that includes Val-8-GLP-1(7-37)OH [see p. 5, line 25]. The X at position 8 can be Val as well as various other residues. Finally, Example 1 describes the Val-8 species used as "chemically synthesized GLP-1(7-37)OH analog having Val substituted for Ala in position 8 (V8-GLP-1)." See p. 16, line 3.

Claim 62 has also been amended to include dimension limitations for the crystals. On page 10, line 1 the Specification provides "The flat rod shaped or plate-like GLP crystals of the present invention, which are prepared using the claimed process, vary in size and shape to some degree. Generally, they range in size from approximately 2-25 microns (μm) by 10-150 μm and are flat, having a depth of approximately 0.5 to 5 μm." In addition, a number of examples describe the crystals produced in terms of dimension. Example 9 describes the crystals as "40 microns long, 15 microns wide, and 3 microns thick." [p. 22, line 20]. Example 10 described the crystals as "10 to 30 microns long and 10 microns wide." [p. 23, line 22]. Example 13 describes the crystals as "150 μm in length, approximately 25 μm wide and less than 5 μm

thick." [p. 25, line 8].

Claims 63 through 67: These claims either directly or indirectly depend from Claim 62. The concentration ranges of peptide, the pH ranges, the ethanol ranges, the zinc concentration and the ammonium sulfate concentration have basis in the original claims as filed as well as throughout the rest of the Specification. For example, original process claim 2 provides a peptide concentration of between 1-10 mg/mL and a pH range between 6 and 7. Original process Claim 3 provides zinc in a molar ratio between 0.5 and 1.7 to peptide and a peptide concentration between 1-20 mg/mL as well as a pH range between 7-10. Additional support in the Specification can be found on pages 11-13. The alcohol concentration is stated as ranging from 2-15% (v/v), preferable 3-13%. Ammonium sulfate concentration is provided as approximately 1% (w/v). [p. 11, lines 19-26]. Peptide concentration ranges of 1-20 mg/mL, preferably 2-10 mg/mL are provided and the total zinc as a molar ratio to peptide is provided as 0.5 to 1.7, preferably 0.6 to 1.5. [p. 12, lines 10-17]. The optimal pH ranges are provided as pH 6-7, preferably 6.4 +/- 0.2 (p. 11, lines 15-16) and as pH 7-10, preferably about 7.2 - 9.7 (p. 12, lines 12-13).

Claims 68-70: These claims are directed to the same crystals of Claim 62 made using a monosaccharide or disaccharide in place of an alcohol. As discussed above, SEQ ID NO:X for Val-8-GLP-1 has been substituted in place of Val-8-GLP-1.

There is clear support for the use of a genus of monosaccharides and disaccharides to make the crystals of the present invention. There are two specific examples describing in detail crystals made using a monosaccharide and a disaccharide (see Applicants response to the Examiner's final rejection pages 4 through 7).

On page 3, line 18 of the Specification the inventors state that "tetragonal flat rod shaped or plate-like crystals . . . could be reproducibly formed from a mother liquor containing a GLP dissolved in a buffered solution and . . . a mono or disaccharide, over a wide range of pH conditions." On

page 12, line 3, the Specification provides that "mono or disaccharides may be substituted for the alcohol in the same ratios on a weight to volume basis." A list of mono and disaccharides suitable for use in making the crystals of the present invention is also provided.

Finally, there are two specific examples wherein Val-8-GLP-1 crystals are made using a monosacchardie or disaccharide. Example 9 on page 22 provides a protocol to make crystals with 5% trehalose (a disaccharide). On line 18, the inventors state that "[a]fter 24 hours V8-GLP-1 crystal clusters and single rectangular crystals were identified." Measurements of these crystals are also provided. Example 10 on page 23 provides a protocol to make crystals with 10% mannitol (a monosaccharide). Measurements of these crystals are also provided.

Claims 69-72: These claims are composition claims and have been amended to comprise the crystals of claims 62 and 68 as well as the addition of zinc to those compositions. On page 4, line 1 the Specification provides: "The crystal compositions of the present invention are pharmaceutically attractive because they are relatively uniform and remain in suspension for a longer period of time than the crystalline clusters or amorphous crystalline suspensions . . . . Most importantly, the crystal compositions of the present invention display extended, uniform, and reproducible pharmacokinetics which can be modulated by adding zinc using conventional crystal soaking techniques or, alternatively, by including zinc in the crystallization solution." Additional support can be found on p. 13, line 15 wherein it is stated: "the invention provides homogenous compositions of individual tetragonal flat rod shaped or plate-like crystal of GLP's. Prior to the processes herein disclosed and claimed, such compositions could not be achieved." Additional support for the addition of zinc is also provided on p. 13, line 24.

TELEPHONIC DISCUSSION WITH THE EXAMINER

On November 3, 2000 a telephonic discussion was held between Mark J. Stewart, Attorney for Applicants, and Examiner

F. Moezie. The Examiner is thanked for her comments during the discussion. The Examiner asked Applicant's attorney to supplement the response sent to the Patent Office on October 20, 2000 and address several specific issues.

1. Crystal Dimensions: The Examiner suggested that Applicant amend the claims to state crystal dimension ranges. Applicants have so amended the claims and point out the support provided in the Specification in the discussion above.

2. The Examiner continued to express concern regarding the substitution of mono- and disaccharides for ethanol or propanol to make the crystals of the present invention. Applicants thoroughly addressed this issue in the prior response to the Examiner's written description and enablement requirements. Applicants reiterate that there is clear support for the use of various sugars both in the Detailed Description as well as in <u>two</u> specific examples wherein crystals are produced using a mono- and a disaccharide and the crystals are described in detail (see discussion above).

3. The Examiner asked the Applicant to check the Sequence Listing filed during prosecution and substitute the proper SEQ ID NO. for the specific GLP-1 peptide encompassed by the claims. Applicants have submitted an updated sequence listing and have made the appropriate amendment.

4. The Examiner also suggested that the Claims wherein zinc is provided as a limitation are not supported by the description because only the addition of $ZnCl_2$ is disclosed. Applicants assert that the addition of zinc is supported by the specification. The inventors focus throughout the specification on the total amount of zinc added not on the amount of one particular zinc salt. On page 12, line 13 the specification discloses adding a specific molar ratio of zinc. "Total zinc, in a molar ratio to GLP, ranges from about 0.5 - 1.7, preferably 0.6

- 1.5." Zinc is discussed in the context of a molar ratio of total zinc. Thus, it is clearly contemplated that zinc can be added in various forms such that the total zinc concentration is within the specified ratio. On page 13, line 6 the inventors state: "Zinc may be added directly to the mother liquor to effect the incorporation of zinc into the crystals." Furthermore, zinc concentrations are always expressed as a mg/mL solution of total zinc. For example on page 20, line 5, the inventors state: "To the crystalline suspensions were added aliquots of a $ZnCl_2$ stock solution (33.4 mg/ml Zn^{++} in buffer A) to make final zinc concentrations either 0.5, 1.0. 1.5, or 2.4 mg/ml zinc." Furthermore, $ZnCl_2$ is not the only source of zinc exemplified. In Example 18 crystals were prepared using a 6.7 mg/ml stock solution of zinc acetate (2-hydrate). [p. 28, line 26].

5. Finally, the Examiner objected to the use of "v/v" and "w/v" as being indefinite. Not only are these terms used consistently throughout the specification, their meaning is clear to a person skilled in the art. The term v/v is volume as percent of total volume and the term w/v is a weight as percent of total volume. In the specification, both the concentration of alcohols and that of ammonium sulfate are expressed as percentages. For example, p. 11, line 23 provides: "The concentration of alcohol ranges from about 2-15% (v/v), preferably 3-13%. . . . Optionally, the addition of approximately 1 % (w/v) ammonium sulfate to the mother liquor will generally increase the yield of crystals." This is further clarified on p. 12, line 3 wherein it is stated that monosachharides or disaccharides may be substituted for the "alcohol in the same ratios on a weight to volume basis." Further, Applicants have attached three different art references which supports Applicant's contention that these terms are clear to a person of skill in the art. In a text entitled "Solubility and Related Properties" by Kenneth James, methods of expressing concentration are discussed. James, K.C.,